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COMPARATIVE STUDY OF PALLIATIVE WHOLE BRAIN RADIATION THERAPY BY 30 GY IN 10 VERSUS 20 GY IN 5 FRACTIONS IN THE TREATMENT OF PATIENTS WITH BRAIN METASTASIS.

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ABSTRACT

Background: A shorter whole brain radiation therapy (WBRT) regimen with 20 Gy in 5 fractions in 5 days would be preferable with 30 Gy in 10 fractions in 2 weeks for patients with brain metastasis. **Methods:** Sixty patients with brain metastasis were enrolled 0ut of which in arm A, 30 patients were treated with 30 Gy in 10 fractions and in arm B, 30 patients received 20 Gy in 5 fractions palliative WBRT. Then the clinical responses were compared between these two arms. **Results:** 65% were male and 35% female among enrolled patients. Median age was 52.7years. 51.67% patient were of initially lung cancer followed by breast carcinoma (26.67%). Histopathology of primary tumor revealed 31.67% of adenocarcinoma, 26.67% of ductal carcinoma, 15% of each small cell carcinoma and squamous cell carcinoma. Majority of brain metastatic lesions were multiple in number (71.67%). Most of the metastatic lesions (93.34%) were located in the cerebral hemisphere. Headache, convulsion and cognitive dysfunction were improved better in short course therapy but nausea and vomiting were improved in standard therapy. Treatment related acute toxicities were more predominant in patients treated with short course therapy. **Conclusion:** Though the short course WBRT with 20 Gy in 5 fractions does increased toxicities it improved clinical response and less time consuming and thus appears preferable in patients with brain metastasis.

KEYWORDS: brain metastasis, whole brain radiation therapy, 20 Gy in 5 fractions, 30 Gy in 10 fractions.

1. INTRODUCTION

Brain metastasis is the most feared cause of morbidity and mortality in cancer patient with the median survival rate is about 2.3 months.[1] Early diagnosis and treatment of brain metastasis result in remission of brain symptoms and enhance the quality of the patient's life and prolong survival.

The most common presenting symptom is headache, focal neurological deficits, cognitive dysfunction, gait ataxia, seizures, speech difficulty, visual disturbance, sensory disturbance.[2] Patients may also present with nausea and vomiting.

Brain metastasis is commonly diagnosed by Computed Tomography (CT) scan and Contrast-enhanced Magnetic Resonance Imaging (MRI) among which MRI is more sensitive when located in the posterior fossa.[3] A peripheral location, spherical shape, ring enhancement with prominent peritumoral edema and multiple lesions all suggest metastatic disease. These characteristics are helpful but not diagnostic, even in patients with a positive history of cancer. Diffusion weighted MRI may be useful for the differential diagnosis of ring-enhancing cerebral lesions.[4,5]

Multivariate analysis revealed that treatment modality is the most significant factor in predicting survival.[6] The Recursive Partitioning Analysis (RPA), developed by the Radiation Therapy Oncology Group (RTOG), categorized patients who received whole brain radiotherapy into one of three prognostic groups. RPA class 1 represented patients younger than 65 years with a Karnofsky's Performance Status (KPS) of at least 70 and a controlled primary tumor with the brain the only site of metastases, resulting in a median survival of 7.1 months. RPA class 3 represented patients with a KPS less than 70, resulting in a median survival of 2.3 months. RPA class 2 represented all other patients, resulting in a median survival of 4.5 months. Graded Prognostic Assessment (GPA) is a newer grading system which has four factors (age, KPS, number of brain metastases and

the status of disease outside the central nervous system) that divided patients into four categories, with median overall survival ranging from 2.6 to11 months.[7] It is important to identify the number of brain metastasis accurately because the treatment strategies differ between patients with one to three metastases compared with those with extensive disease. Treatment decisions may also be influenced by prognostic factors - performance status, age and extent of extra cranial disease.[8]

Brain metastasis is rarely curable and the intention of treatment is palliative, designed to prevent disability and suffering and if possible, to prolong life. The goal of treatment is rapid control of symptoms and durable symptom-free remission. Without treatment, the median survival is 1 month.[9]

Definitive treatment options continue to evolve and include whole brain radiotherapy, surgery and stereotactic radio surgery (SRS). Patients with multiple metastases are treated with whole brain radiotherapy alone.[1] Median survival after whole brain radiotherapy is 3–6 months. Different fractionation schedules, ranging from 20 Gy in 1 week to 50 Gy in 4 weeks, yield comparable results with good palliation of symptoms including headache, motor deficits, confusional states and cranial nerve palsies.[10,11] Hypofractionated treatments are generally employed, most commonly 30 Gy in 10 fractions or 20 Gy in 5 fractions.[6]

Till date, only a few studies have compared short-course whole brain radiotherapy with long-course whole brain radio therapy for the treatment of patients with brain metastasis.[12,13,14,15,16] Short-course whole brain radiotherapy with20 Gy in 5 fractions resulted in survival and local control that were similar to longer programs in patients with brain metastases. The dose of 20 Gy in 5 fractions appears preferable for the majority of these patients because it is less time consuming and more convenient.

The optimal dose fractionation of whole brain radiotherapy is still controversial. The majority of patients with brain metastases have an extraordinarily poor survival prognosis. For these patients, whole brain radiotherapy with a short overall treatment time would be preferable to longer whole brain radiotherapy programs because it is more convenient for these often-debilitated patients with limited life span. Furthermore, longer palliative radiotherapy programs may increase the cost of therapy without improving efficacy, as has been demonstrated for other palliative situations.[17]

In the study short-course whole brain radiotherapy with 20 Gy in5 fractions given within 5 days was compared with long-course whole brain radio therapy with 30 Gy in 10 fractions given over 2 weeks in brain metastasis patients by seeing the clinical response by relief of symptoms and acute side effects. In a third world country like Bangladesh, we are always with a huge patient burden due to the lack of machines. If we can treat these brain metastatic patients with this shorter time schedule, definitely it will cut the patient queue in radiotherapy department. The dose of 20 Gy in 5 fractions will be preferable for the majority of these patients because it is less time consuming, less expensive and more convenient.

Brain metastasis is being an emerging problem to our country needs further study and evaluation to choose the best treatment which will be highly effective. So far, our knowledge goes; no substantial works has been carried out in this area in Bangladesh. This study will hopefully open a new horizon in this field of oncology and may give us information about the proper management of brain metastasis.

2. MATERIALS AND METHOD

This observational prospective hospital based study was conducted during the period of July 2011 to June 2012 and was carried out in Department of Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Department of Radiation Oncology, National Institute of Cancer Research & Hospital, Dhaka, and Department of Radiotherapy, Dhaka Medical College & Hospital, Dhaka, Bangladesh. Ethical approval was obtained from the ethical review committee of Bangabandhu Sheikh Mujib Medical University, Dhaka. Sixty hospital-based patients with histologically or cytologically proven malignant disease with radiologically proven brain metastasis treated with 30 Gy in 10 fractions in 2 weeks and those compared with another group treated with 20 Gy in 5 fractions in 5 days and had any part of their treatment were enrolled in the study and were convinced to participate in the study after giving written informed consent and satisfying inclusion and exclusion criteria. Non-probability convenient and purposive sampling was done. Patients were evaluated carefully and the particulars of the patients including history, clinical examination and investigations were taken in the prescribed form and noted in the data sheet.

2.1 Inclusion criteria

1. Histologically or cytologically proven malignant disease with radiologically proven brain metastasis.
2. No history of previous cranial radiotherapy.
3. Age from 18 to 70 years.
4. Karnofsky Performance Status (KPS) >70.
5. Adequate hematologic, hepatic and renal function.
6. Able to provide written informed consent.

2.2 Exclusion criteria

1. Patients with primary brain tumor and CNS lymphoma.
2. Brain metastasis due to germ cell tumor.
3. Serious concomitant medical illness including severe heart disease, uncontrolled diabetes mellitus or hypertension.
4. Patient with uncontrolled infection.

5. A medical or psychiatric condition that compromises ability to give informed consent or complete the protocol.
6. Pregnant or lactating woman.

2.3 Criteria for discontinuation of treatment

1. Patient's refusal to continue study participation.
2. Occurrence of unacceptable toxicity necessitating major modification of treatment.

2.4 Pretreatment evaluation

Following procedures were followed to evaluate the patient's condition before treatment.

- Complete history and physical examination.
- Location and size of lesions were recorded prior to treatment.
- Histopathological examination reports, which has already been done by taking biopsy from primary site.
- Laboratory studies.
  - CBC with differential and platelet count.
  - Kidney function test.
  - Liver function test.
- Radiological studies.
  - CT scan orMRI of the brain with contrast.
  - X-ray chest P/A view and USG of whole abdomen.

2.5 Treatment planning

Whole brain irradiation was given by parallel opposed pair of lateral fields using cobalt or LINAC machine. Conventional fraction i.e. one fraction per day, five days per week, was used. During the treatment planning the information required were total dose to target volume, number of fractions, dose per fraction and overall time for treatment. After verification of field arrangements, the treatment prescription was finalized and signed. Target volume was decided with the aid of CT scans or MRI of Brain. Treatment area was marked on the skin with gentian violet placing the patient on the table. Patient's position was correlated with the position of the patient at the machine during treatment. Simulation is not essential and anatomical landmarks of the base of skull (a line from outer canthus to the external auditory meatus) to mastoid can be used Anatomical landmarks and the field sizes were noted on the radiation therapy card.

2.6 Patient assessment

Assessment during treatment

During treatment, the patients were assessed weekly for treatment response and side effects. Duration of treatment was measured from the first day of treatment to the last date of treatment.

Relief of symptoms: Headache, nausea, vomiting, convulsion and cognitive dysfunction were the major complaints that were taken as parameters of symptoms. Symptomatic response was assessed and compared with the pre-treatment conditions.

Toxicities reporting: The common toxicity criteria (The national cancer institute's "Common terminology criteria for adverse events, v.3.0." published on June 10, 2003) was used to score acute toxicities. Toxicities were assessed after each fraction of WBRT. 'Acute toxicities' are acute reactions following treatment and are rapid in onset and typically reversible. These occur from day1 of commencement of therapy to day 90 (RTOG definition).

Assessment after treatment

After completion of treatment patients were carefully supervised to attain first follow-up one week after the end of treatment. Follow up was performed weekly, i.e. 1st, 2nd, 4th and 8th weeks after completion of radiation during the research period. At each follow-up clinical examination and associated laboratory investigations were done and the effect of radiotherapy as relief of symptoms and toxicities due to radiotherapy were recorded.

2.7 Measures of outcome variables

The outcome variables were studied: Age, Sex, Socioeconomical status, Occupational status, Educational status, Primary tumor site, histopathology of primary tumor, Number of metastatic lesion, Performance status, Clinical presentations such as Headache, nausea, vomiting, convulsion &cognitive dysfunction and treatment related toxicities such as: Fatigue, skin reaction, hair loss & mucositis.

2.8 Statistical analysis

The data was tabulated in separate tables for both Arm-A & Arm-B. Data analysis was done according to the objectives of the study by using the Statistical Package for Social Science (SPSS) software program for windows version 13.0 available in the institute.

3. RESULTS

All the 60 patients of brain metastasis were above 20 years among which 21 (35%) patients were in the age group of 50-59 years. Mean age 52±11.4 years in arm A and 53.4±10.56 years in arm B. Number of male and female patients were 39 (65%) and 21 (35%) respectively with the ratio of 1.86: 1 indicating male predominance. Regarding the economic status, 48.33% were from poor class, 40% were in middle class and 11.33% were in higher class.

In arm A, among 30 patients 16 were from lung cancer, 8 from breast cancer, 2 from carcinoma of unknown primary site, 1 from sarcoma and 3 were from other primary malignancy. In arm B, among 30 patients 15 were from lung, 8 from breast cancer, 3 from carcinoma of unknown primary, 1from sarcoma and 3 were from other primary malignancy (Figure 1).

In arm A, out of 30 patients 9 adenocarcinoma, 8 duct cell carcinoma, 5 small cell carcinoma, 5 Squamous cell carcinoma, 1 sarcoma,1 renal cell carcinoma and 1transitional cell carcinoma were found. In arm B,10

adenocarcinoma, 8 duct cell carcinoma, 4 small cell carcinoma,4 squamous cell carcinoma, 1 sarcoma,1 papillary carcinoma of thyroid, 1 adenoid cystic carcinoma and1 melanoma were found (Figure:2).

Out of 60 patients, most of the brain metastatic lesions were located in the cerebral hemisphere with 27/30 in arm A and 29/30 in arm B. (Figure: 3).

The number of metastatic lesions of studied population was shown in figure 4. In arm A, 7 were solitary metastatic lesion and 23 were multiple metastatic lesions. In arm B, 10 were solitary metastatic lesion and 20 were multiple metastatic lesions.

Regarding the performance status, all patients were between 90 to70 KPS. In arm A, before starting the treatment, 2 patients were found with KPS 90 where in arm B, 3 patients were found with the same performance status. After completion of the RT, improvement was noticed in the performance status with 4 patients in arm A and 5 patients in arm B with KPS90. Before RT, 7 patients were with KPS 80 in arm A and 8 in arm B and after completion of the RT it was found in 10 and 12patients respectively. Before RT, 21 patients were found with KPS 70 in arm A and 19 in arm B and after completion of the treatment it was found 16 and 13 respectively (Table 1).

Table 2 shows the overall response rate to treatment. In case of headache, response rate were reported 78% in arm A and 85% in arm B. In case of nausea and vomiting, the response rates were 85% and 87% in arm A and 75% and 82% in arm B respectively. In case of convulsion and cognitive dysfunction, the response rates were 82% and 85% in arm A and 87% and 92% in arm B respectively.

Table 3 shows the treatment related acute toxicities. Fatigue, skin reaction (Grade I-III), hair loss (Grade I-II), mucositis (Grade I) was more predominant in patients treated with 20 Gy in 5 fractions.

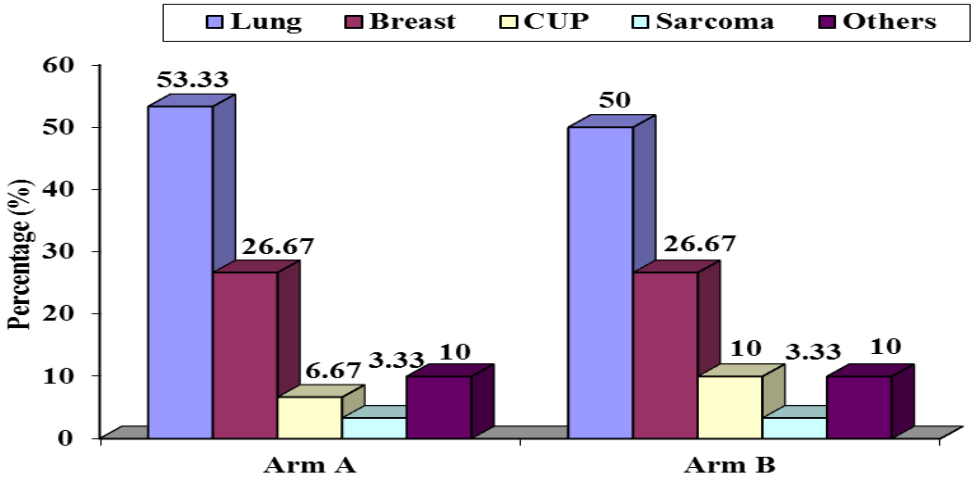

Figure 1: Distribution of the patients by Primary tumor site.

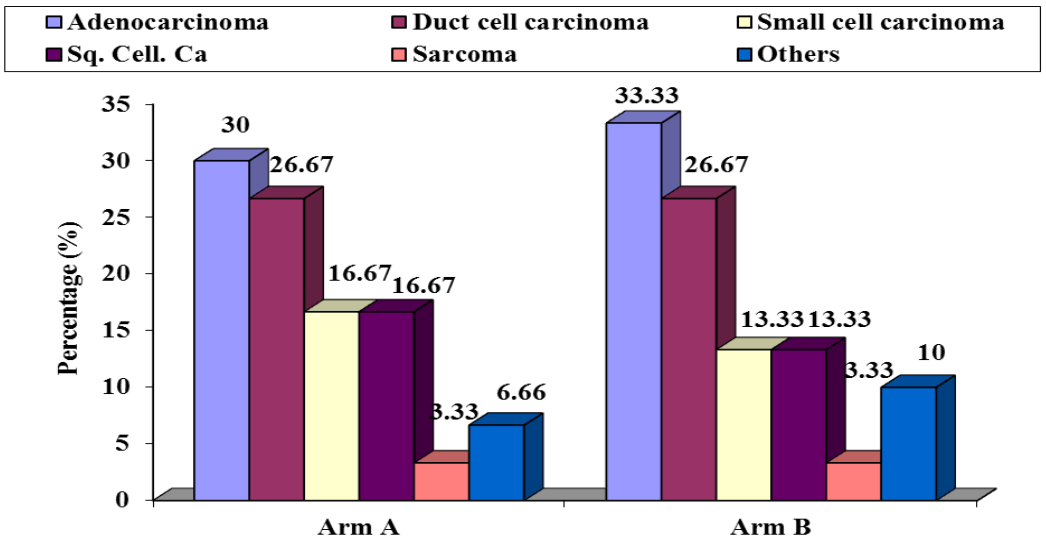

Figure 2: Distribution of the patients by Histopathology of primary tumor.

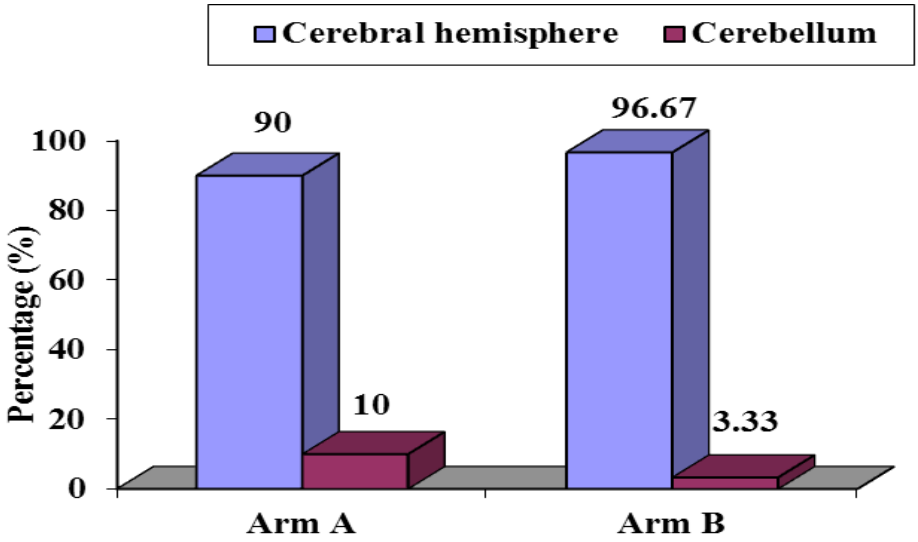

Figure 3: Distribution of patients according to Location of metastatic tumor.

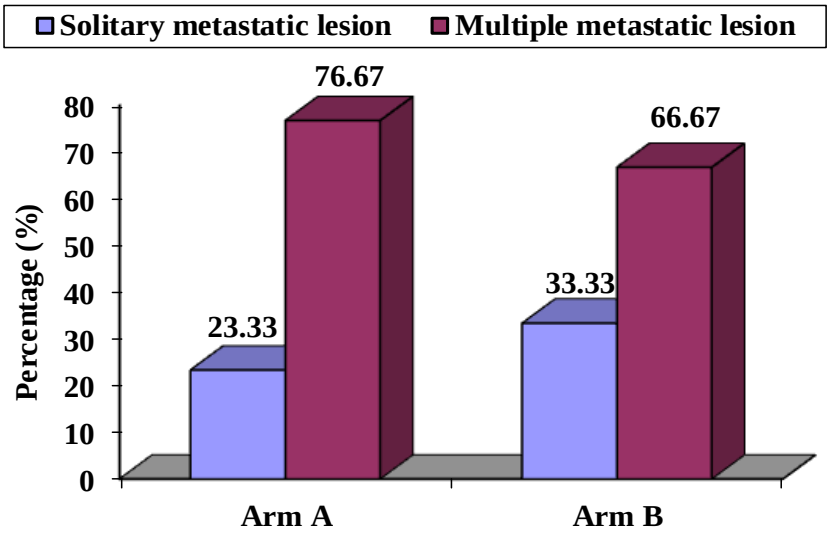

Figure 4: Distribution of the patients by Number of Metastatic Lesion.

Table 1: Distribution of patients according to Performance status.

Performance status (KPS)	Treatment Group	Before RT		After RT	
		n	%	n	%
90	Arm A	2	6.67	4	13.33
	Arm B	3	10.00	5	16.67
80	Arm A	7	23.33	10	33.33
	Arm B	8	26.67	12	40.00
70	Arm A	21	70.00	16	53.33
	Arm B	19	63.33	13	43.33
Total	Arm A	30	100	30	100
	Arm B	30	100	30	100

Table 2: Principal presenting symptoms and overall response to treatment.

Symptoms	Treatment Group	Before RT		After RT		Response (%)	x^2	P value
		n	%	n	%			
Headache	Arm A	28	93.33	6	20.00	78	0.280	0.596
	Arm B	27	90.00	4	13.33	85		
Nausea	Arm A	26	86.67	4	13.33	85	0.511	0.475
	Arm B	28	93.33	7	23.34	75		
Vomiting	Arm A	24	80.00	3	10.00	87	0.211	0.646
	Arm B	22	73.33	4	13.34	82		
Convulsion	Arm A	17	56.67	3	10.00	82	0.125	0.723
	Arm B	16	53.33	2	6.67	87		
Cognitive dysfunction	Arm A	13	43.33	2	6.67	85	0.232	0.630
	Arm B	12	40.00	1	3.33	92		

Table 3: Distribution of treatment related toxicities in arm A and arm B.

Toxicities	Arm A		Arm B		Total		x2	P value
	n	%	n	%	N	%		
i. Fatigue	**21**	**70.00**	**25**	**83.33**	**46**	**76.67**	1.491	0.222
ii. Skin reaction								
Grade 1	8	26.67	11	36.67	19	31.67	0.007	0.932
Grade II	2	6.67	3	10.00	5	8.33		
Total	**10**	**33.34**	**14**	**46.67**	**24**	**40.00**		
iii. Hair loss								
Grade 1	7	23.33	10	33.33	17	28.33	0.065	0.798
Grade II	1	3.33	2	6.67	3	5.00		
Total	**8**	**26.66**	**12**	**40.00**	**20**	**33.33**		
iv. Mucositis								
Grade I	**8**	**26.67**	**11**	**36.67**	**19**	**31.67**	0.693	0.405

4. DISCUSSION

Brain metastasis is a common site of distant failure for malignancies. The optimal management of brain metastases often necessitates the combination of multiple therapeutic modalities, including surgery, radiation therapy, chemotherapy, steroid therapy and radiosurgery. The trend has been continuously changed along with the advancement of cancer management, development of new technology and changing in perception of quality of life.

This prospective observational study was carried out with an aim to compare the effect of short-course whole brain radiotherapy with 20 Gy in 5 fractions given within 5 days with long-course whole brain radiotherapy with 30 Gy in 10 fractions given over 2 weeks in brain metastatic patients.

In the present study, primary tumor site of studied population was shown that 31 (51.67%) of patients of primary lung cancer, 16 (26.67%) of breast cancer, 5(8.33%) of carcinoma of unknown primary which is relatively similar with one study that showed 47% of metastatic brain tumor were lung origin and 21% of breast origin.[18] Histopathology of primary tumor of studied population was shown that 19 (31.67%) patients were of adenocarcinoma, 16(26.67%) of duct cell carcinoma, 9(15%) of each small cell carcinoma and squamous cell carcinoma which is similar with one study that showed 34 % of metastatic brain tumor were adenocarcinoma, 14% of duct cell carcinoma and 7% of small cell carcinoma.[19]

Study revealed that in majority of brain metastatic patients, the lesion was located in the cerebral hemisphere 56(93.33%) and 4 (6.67%) were in the cerebellum. The study also demonstrates that 17 (28.33%) of brain metastasis was solitary lesion and 43 (71.67%) were of multiple lesions. In one study, result showed that 36% was of solitary brain lesion and 64% were of multiple lesions.[19]

All the patients in this study were with KPS > 70, among them most of the patient were of KPS 70(66.67%), 15 (25%) were of KPS 80 and 5 (8.33%) were of KPS 90 and performance status was more improved with 20 Gy in 5 fractions shorter course radiotherapy and thereby, improved quality of life in the shorter course radiotherapy patients. The most common symptoms associated with brain metastasis were headache, convulsion, nausea, vomiting and cognitive dysfunction. All presenting symptoms except nausea and vomiting are more responding with the short course WBRT comparing to the long course WBRT. These findings were similarly found in others study.[20] Regarding treatment related acute toxicities of the studied patients were more predominant in patients treated with 20 Gy in 5 fractions. In one study, it was found that fatigue, skin reaction, hair

loss and scalp irritation are the acute toxicities of palliative WBRT.[21] Considering all these advantages and disadvantages, this study revealed that shorter course WBRT with 20 Gy in 5 fractions in 5 days can effectively achieve response in metastatic brain tumor patients. The short course WBRT with 20 Gy in 5 fractions results in improved clinical response by relief of symptoms but does increased toxicities compared with the standard treatment of 30 Gy in 10 fractions in patients with brain metastasis.

5. Limitations of the study

In this study, all relevant examinations such as CT scan based follow up which could play significant role in the assessment of clinical outcome of patients could not be possible by the patients due to financial constrain.

6. CONCLUSION

Though there were some limitations of the study, treatment of brain metastasis with 20 Gy in 5 fractions in 5 days shows a considerable promise. However, further research is required to determine the treatment outcome and evaluation of toxicities after long-term follow up with a large sample size of patients with brain metastasis. In a developing country like Bangladesh, we are always with a huge patient burden due to the lack of machines. If we can treat these brain metastatic patients with this shorter time schedule, definitely it will cut the patient queue in radiotherapy department.

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